Patent
233.US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#16
APPD
5-28-03

Applicant	:Weeks
Application No.	:09/554,951
Filed	:November 27, 2000
For	: THE USE OF Δ5-ANDROSTENE-3β-OL-7,17-DIONE IN THE TREATMENT OF ARTHRITIS
Examiner	:Hui, San-ming
Group Art Unit	:1617

APPEAL BRIEF IN TRIPLICATE UNDER 37 C.F.R. § 1.192

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to the Final Office Action, dated July 16, 2002, the Advisory Action, dated January 29, 2003, and the Notice of Appeal, dated December 13, 2002, for the above-referenced application, the following timely Appeal Brief in triplicate is respectfully submitted.

Authorities

Patents

Lardy, U.S. Patent No. 5,585,371

Peat, U.S. Patent No. 4,628,052

Cases

Brenner v. Manson, 148 U.S.P.Q. 689 (C.C.P.A. 1966)

In re Fine, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988)

In re Geisler, 116 F.3d 1465, 43 U.S.P.Q.2d 1362 (Fed. Cir. 1977)

In re Jones, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992)

In re Merck & Co., Inc., 800 F.2d 1091, 231 U.S.P.Q. 375 (Fed. Cir. 1986)

Ortho Pharmaceutical Corp. v. Smith, 22 U.S.P.Q.2d 1119 (Fed. Cir. 1992)

In re Royka, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974)

In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991)

Real Party in Interest

Humanetics Corporation, a corporation with its principle place of business at Interchange Tower, Suite 1205, 600 South Highway 169, St. Louis Park, MN 55426-1205 is the Real Party in Interest.

1. Related Appeals and Interferences

No other appeals or interferences are known to appellant, appellant's legal representative, or assignee that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

2. Status of Claims

Claims 1-11 and 22-38 are pending. Claims 1-11 and 22-38 stand rejected.

The rejection of claims 1-11, 22-29, 31 and 32 is hereby appealed.

3. Status of Amendments

The proposed amendments provided in the Response to Final Office Action, dated December 13, 2002, were not entered. The claim objections under 37 C.F.R. § 1.75(c), and the claim rejections under 35 U.S.C. § 112, second paragraph and 35 U.S.C. § 103(a), remain.

4. Summary of Invention

The instant invention is drawn to methods of treating or preventing arthritis using Δ5-androstene-3β-ol-7,17-dione and 3β esters thereof. (See, the "Summary of Invention", page 4, lines 8-12; and the "Detailed Description of the Invention" page 4, lines 18-22 and page 5, lines 4-11).

5. Issues

Whether claims 22-29, drawn to methods of treating or preventing arthritis using Δ5-androstene-3β-ol-7,17-dione and 3β esters thereof, in which the one or more symptoms of arthritis are limited to those symptoms selected from the group consisting of tissue inflammation, joint pain, joint stiffness, inability to move a joint normally, nodules, and swelling, are unpatentable under 37 C.F.R. § 1.75(c) for failing to further limit the method recited in claim 1 or 2, in which the one or more symptoms of arthritis are not limited.

Whether claims 7, 11 and 26, drawn to methods of treating or preventing arthritis using Δ5-androstene-3β-ol-7,17-dione and 3β esters thereof, in patients that are either afflicted or diagnosed with arthritis-related tissue inflammation, are unpatentable under 35 U.S.C. § 112, second paragraph, for indefiniteness as to what patients are encompassed by the claims.

Whether claims 1-11, 22-29, 31 and 32, drawn to methods of treating or preventing arthritis using Δ5-androstene-3β-ol-7,17-dione and 3β esters thereof, are unpatentable under 35 U.S.C. § 103(a) for obviousness based on the disclosure in Lardy (U.S. Patent No. 5,585,371) in view of Peat (U.S. Patent No. 4,628,052).

6. Grouping of Claims

All of the claims stand or fall together.

7. Argument

<u>The Claimed Invention is in Proper Dependent Form under 37 C.F.R. § 1.75(c)</u>

Claims 22-29, drawn to methods of treating or preventing arthritis using Δ5-androstene-3β-ol-7,17-dione and 3β esters thereof, in which the one or more symptoms of arthritis are limited to those symptoms selected from the group consisting of tissue inflammation, joint pain, joint stiffness, inability to

move a joint normally, nodules, and swelling, are in proper dependent form under 37 C.F.R. § 1.75(c), because they further limit the method recited in claim 1 or 2, in which the one or more symptoms are not limited.

The Examiner states that "The method of claim 22 is directed to a method of treating arthritis, i.e., the inflammation of the joint. "Tissue inflammation" as recited in claim 22 encompasses inflammatory sites other than joints and thus, fail[s] to further limit the preceding claim." See, Paper 11, page 3, lines 13-15.

This argument fails for at least two reasons: (1) arthritis includes inflammation at sites other than the joint, and (2) "tissue inflammation" is a subset of the many possible "one or more symptoms of arthritis" and so further limits the preceding claim.

A. Arthritis is Not Limited to Joint Inflammation

A "method of treating arthritis" is broader than a "method of treating the inflammation of the joint". The specification states that "Arthritis is a collective term for a number of different conditions that cause pain, swelling and limited movement in joints and connective tissue throughout the body." See, the Specification, page 1, lines 14-15, Emphasis added. Although osteoarthritis is linked to specifically to joint disease and the breakdown of the joint's cartilage, "Fibromyalgia (FM) is manifest as widespread pain affecting muscles and attachments to the bone." See, the Specification, page 1, lines 26-27 and page 2, lines 11-12, Emphasis added. Further, the autoimmune disorder aspect of rheumatoid arthritis "is generally characterized by inflammation of the membrane lining the joint." See, the specification, page 2, lines 20-22, Emphasis added.

Thus, arthritis is not limited to joint inflammation, but encompasses tissue inflammation at sites other than the joints, including connective tissue, muscles, attachments to bone, and membrane linings.

B. Tissue Inflammation Further Limits One or More Symptoms

Independent claim 1 states in part, "wherein said administration results in amelioration or prevention of one or more symptoms of arthritis." Dependent claim 22 states in part, "wherein said one or more symptoms of arthritis are selected from the group consisting of tissue inflammation, join pain, joint stiffness, inability to move a joint normally, nodules, and swelling." Claims 23-29 depend from claim 22. See, Appendix.

The fact that arthritis is not limited to joint inflammation, but also encompasses other forms of tissue inflammation has been discussed above (Section A). In addition, symptoms of arthritis include far more than just tissue inflammation, including, but not limited to, "pain, swelling and limited movement", "fatigue, sleep disturbances, migraine headaches, irritated bowel syndrome, chest pain and nervous system symptoms", and "nodules under the skin." See, the Specification, page 1, lines 14-15 and page 2, lines 13-15 and 31.

Therefore, dependent claims 22-29 further limit claim 1 or 2, and therefore the objection should be withdrawn and the claims allowed.

The Claimed Invention is Not Indefinite under 35 U.S.C. § 112, Second Paragraph

Claims 7, 11 and 26, drawn to methods of treating or preventing arthritis using Δ5-androstene-3β-ol-7,17-dione and 3β esters thereof, in patients that are either afflicted or diagnosed with arthritis-related tissue inflammation, are not indefinite under 35 U.S.C. § 112, second paragraph, because it is clear which patient populations are encompassed by the claims.

The Examiner states that "It is not clear what tissue inflammation conditions are encompassed by the expression herein and therefore, it is not clear what patient populations are encompassed hereby." See, Paper 11, page 4, lines 3-5 and 8-10.

This argument fails, because it is clear from the claim language (arthritis-related tissue inflammation) that the tissue inflammation conditions are those related to arthritis. Thus, the patient populations are those arthritis patients with tissue inflammation related to their arthritis.

Claims 7, 11, and 26 are ultimately dependent on claim 1, which states in part, "A method of treating or preventing arthritis in a patient in need of such treatment or prevention." Claims 7, 11 and 26 all further limit the patients described in claim 1, to a patient either diagnosed or afflicted with "arthritis-related tissue inflammation." See, Appendix.

Thus, all of these patients are defined by their need for arthritis treatment or prevention according to claim 1, and then are further defined in the dependent claims by the fact that they are either afflicted or diagnosed with tissue inflammation related to their arthritic condition. As a result, claims 7, 11 and 26 clearly identify the claimed subject matter, and therefore the rejections under 35 U.S.C. § 112, second paragraph, for indefiniteness should be withdrawn and the claims amended.

The Examiner has Failed to Prove
a *Prima Facie* Case of Obviousness under 35 U.S.C. § 103(a)
Based on the Disclosure in Lardy in View of Peat

Claims 1-11, 22-29, 31 and 32, drawn to methods of treating or preventing arthritis using Δ5-androstene-3β-ol-7,17-dione and 3β esters thereof, are patentable and are not obvious under 35 U.S.C. § 103(a) based on the disclosure in Lardy (U.S. Patent No. 5,585,371) of a comparison of the immunological activity of Δ5-androstene-3β-ol-7,17-dione and dehydroepiandrosterone (DHEA) and in view of the disclosure in Peat (U.S. Patent No. 4,628,052) of the utility of DHEA for osteoarthritis, rheumatoid arthritis, and non-specific joint pain.

Three criteria must be met to establish a case of *prima facie* obviousness: (1) there must be some suggestion or

motivation to modify or combine references, (2) there must be a reasonable expectation of success, and (3) the references must teach or suggest all the claim limitations. The teaching or suggestion to make the combination and the reasonable expectation of success must both be found in the cited art, not the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

A reasonable reading of the cited references (Lardy and Peat) indicates that taken together they satisfy none of the three criteria stated above.

I. Lardy and Peat do Not Teach or Suggest All the Claim Limitations.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974).

The claimed invention is drawn *inter alia* to methods of treating arthritis by administering Δ5-androstene-3β-ol-7,17-dione and β esters thereof. These compounds are essentially incapable of being metabolized to androgens, estrogens or DHEA See, for example, the Specification, page 4, lines 18-22.

These claim limitations are neither taught nor suggested by the cited art.

A. The Cited Art Does Not Teach All Claim Limitations

The Examiner states that "Lardy does not expressly teach that [Δ5-androstene-3β-ol-7,17-dione] is useful in a method to treat arthritis such as osteoarthritis, fibromyalgia, and rheumatoid arthritis. Peat teaches that DHEA is useful in a method of osteoarthritis, rheumatoid arthritis, and non-specific joint pain." See, Paper 11, page 5, lines 4-7.

Taken together, these statements show that the Examiner acknowledges that the cited art does not teach treating arthritis

by administering Δ5-androstene-3β-ol-7,17-dione and β esters thereof. Thus, the requirement for teaching all claims limitations is not met.

B. The Cited Art Does Not Suggest All Claim Limitations

In addition to not teaching all the claim limitations, the cited art does not suggest all the claim limitations. Moreover, the Examiner does not provide a reasoned explanation for how the cited art taken together allegedly suggests all the claim limitations.

However, taken together, Peat and Lardy, at most, teach treating arthritis using DHEA, a compound DHEA with significant androgenic ability and some immune stimulating ability. DHEA is the major androgen precursor in men and women. See, for example, the Specification, page 3, lines 21-22. DHEA has some ability to improve antibody responsiveness of the immune system. See, for example, Lardy, column 10, lines 31-33. DHEA is taught for osteoarthritis, rheumatoid arthritis, and non-specific joint pain. See, Peat, abstract.

Therefore, taken together, Peat and Lardy do not suggest using Δ5-androstene-3β-ol-7,17-dione for arthritis. Δ5-androstene-3β-ol-7,17-dione, unlike DHEA, does not have significant androgenic ability. See, for example, the Specification, page 4, lines 18-22. Further, Δ5-androstene-3β-ol-7,17-dione, unlike DHEA, has superior immunologic activity. See, for example, Lardy, column 10, lines 31-33.

Thus, Lardy and Peat do not teach or suggest all the claim limitations of a method to treat or prevent arthritis using a compound without androgenic potential and with immuno-stimulatory potential. Therefore, the Examiner has failed to make a prima facie case for obviousness, and this rejection cannot stand.

II. Lardy and Peat Provide No Suggestion or Motivation to Modify or Combine References.

Obviousness can only be established by combining or modifying teachings where there is some teaching, suggestion or motivation to do so found either in the reference or in the general knowledge of one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992).

The Examiner states that, "It is known that both DHEA and [Δ5-androstene-3β-ol-7,17-dione] have similar immunological effect[,] and based on Lardy, DHEA is known to be useful in [a] method of treating [the] painful condition of osteoarthritis and rheumatoid arthritis." *See*, Paper 11, page 5, lines 11-15.

This argument fails because the Examiner has mischaracterized the cited art. In fact, Lardy teaches that Δ5-androstene-3β-ol-7,17-dione has superior immunologic activity compared to DHEA.

A fair reading of Lardy provides objective evidence that DHEA and Δ5-androstene-3β-ol-7,17-dione do not function similarly as immune response affecting agents. In Example VI (Immune System Response of Δ5-androstene-3β-ol-7,17-dione), the data show that treatment with Δ5-androstene-3β-ol-7,17-dione decreased mortality from a herpes infection to 26%, while DHEA treated animals showed little to no difference from untreated control animals (67% compared to 80%). Under "Conclusions," Lardy writes, "Administration of Δ5-androstene-3β-ol-7,17-dione substantially enhances immune response relative to normal response. Δ5-androstene-3β-ol-7,17-dione is also substantially superior to DHEA in enhancement of immune system response." See, Lardy, column 10, lines 1-33.

Clearly, a compound that acts in a superior manner to another compound does not function similarly, and so this motivation to modify or combine references fails. Therefore, the

cited art does not provide a suggestion or motivation to modify or combine references to achieve the claimed method to treat or prevent arthritis using a compound with superior immuno-stimulatory potential. Therefore, the Examiner has failed to make a prima facie case for obviousness, and this rejection cannot stand.

III. Lardy and Peat do Not Indicate that there is a Reasonable Expectation of Success.

The cited art can be modified or combined to reject claims as *prima facie* obvious only if there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 U.S.P.Q. 375 (Fed. Cir. 1986).

The Examiner states that, "Employing [Δ5-androstene-3β-ol-7,17-dione], a structurally similar compound [that] also has similar pharmacological activities as DHEA, in the same method [as] Peat to treat arthritis...would have been reasonably expected to be similarly effective." See, Paper 11, page 5, lines 15-18.

This argument fails for at least two reasons: (1) because steroid hormone activity can be structure specific, and (2) because DHEA and Δ5-androstene-3β-ol-7,17-dione have different pharmacological activities.

A. Steroid Hormone Activity can be Structure Specific

Steroid hormone activity can be structure specific, such that the activity of structurally related species can be difficult to predict. *See, for example, Ortho Pharmaceutical Corp. v. Smith*, 22 U.S.P.Q. 1119, 1125 (1992) and *Brenner v. Manson*, 148 U.S.P.Q. 689, 694 (1966). Here, the difference between DHEA and Δ5-androstene-3β-ol-7,17-dione is the addition of a ketone at the 7 position. This chemical change results in a compound with no significant androgenic or estrogenic activity, and superior immunological activity as compared to DHEA, that

lacks the ketone at the 7 position (see further discussion below, Section B). Thus, the structural similarity, without more, does not make a *prima facie* case of obviousness.

B. The Pharmacological Activity of DHEA is Different from Δ5-androstene-3β-ol-7,17-dione

The pharmacologic activity of DHEA differs from that of Δ5-androstene-3β-ol-7,17-dione in at least two respects: (1) DHEA is far less active immunologically than Δ5-androstene-3β-ol-7,17-dione, and (2) DHEA has significant androgenic and estrogenic activity that is lacking in Δ5-androstene-3β-ol-7,17-dione.

The superiority of Δ5-androstene-3β-ol-7,17-dione over DHEA immunologically (based on Lardy) have been discussed at length above (Section II). Clearly, a compound that is immunologically superior to another compound, will not be expected to have similar pharmacological effects.

A known pharmacological activity of DHEA is as an androgen and estrogen precursor. DHEA is the major androgen precursor in men and women. See, for example, the Specification, page 3, lines 21-22. Unlike DHEA, Δ5-androstene-3β-ol-7,17-dione does not have significant androgenic ability. See, for example, the Specification, page 4, lines 18-22. Clearly, a compound that is not appreciably metabolized to androgens, will not be expected to have similar pharmacological effects as a compound that is the major androgen precursor.

Thus, taken as a whole, the cited art does not indicate a reasonable expectation of success. Thus, the requirement for making a prima facie case of obviousness has not been met.

IV. The Art Teaches Away from the Claimed Invention

A *prima facie* case of obviousness can also be rebutted by showing that the art, in any material respect, teaches away from

the claimed invention. *In re Geisler*, 116 F.3d 1465, 1471, 43 U.S.P.Q.2d 1362, 1366 (Fed. Cir. 1977).

Here, the art teaches away in at least two material respects: (1) DHEA's usefulness for treating arthritis would be predicted to relate to its androgenic or estrogenic activity, which is absent in Δ5-androstene-3β-ol-7,17-dione, and (2) Δ5-androstene-3β-ol-7,17-dione's superior immunological activity, compared to DHEA, would be counter-intuitive for treating arthritis.

A. Lack of Significant Androgenic or Estrogenic Activity Teaches Away

DHEA is the major androgen precursor in humans, and is responsible for pleiotropic effects in humans. Δ5-androstene-3β-ol-7,17-dione is not significantly metabolizable to androgens, including DHEA, and does not have androgenic effects in humans. See, for example, the Specification, page 3, lines 21-22 and page 4, lines 18-22.

Since low androgen levels have been linked to arthritis, a compound that raised androgen levels (like DHEA) would be predicted to be beneficial. In contrast, the lack of androgenic activity resulting from Δ5-androstene-3β-ol-7,17-dione administration would teach away from its use in arthritis.

In rheumatoid arthritis (RA), for example, androgen levels are low in both men and women. In addition, RA is characterized by striking age-sex disparities. The incidence of RA in women increases steadily from the age of menarche to its maximal incidence around menopause. The disease is uncommon in men under 45, but its incidence increases rapidly in older men and eventually approaches the incidence in women. These events correlate with dramatic changes in androgen levels in men and women. These observations strongly suggest that androgens may play some role in RA. See, for example, the Specification, page 3, lines 16-31.

Furthermore, since elevated levels of female sex hormones (estrogens) have been linked to remission of arthritis in pregnancy, a compound that raised estrogenic levels (like DHEA) would be predicted to be beneficial. Moreover, DHEA itself has been found to be present in elevated quantities during pregnancy, providing additional reason to predict benefit. See, Peat, column 1, lines 36-46. In contrast, the lack of estrogenic activity resulting from Δ5-androstene-3β-ol-7,17-dione administration would teach away from its use in arthritis.

Thus, one of ordinary skill in the art would be likely to conclude that DHEA's activity in arthritis may well be the result of its androgenic or estrogenic ability. Since Δ5-androstene-3β-ol-7,17-dione lacks androgenic and estrogenic activity, Peat teaches away from the use of Δ5-androstene-3β-ol-7,17-dione to treat arthritis.

B. Superior Immunological Activity Teaches Away

Enhancing immune function and particularly improving the immune response to an antigen, is counterintuitive as a treatment for arthritis. Arthritis is a disorder with inflammatory components. It is typically treated with anti-inflammatory drugs. See, the Specification, page 2, lines 4-9 describing conventional treatment for osteoarthritis; page 2, lines 17-18 describing conventional treatment for fibromyalgia; and page 3, lines 8-14 describing conventional treatment for rheumatoid arthritis. Further, rheumatoid arthritis has an autoimmune aspect "generally characterized by inflammation of the membrane lining the joint resulting from an attack upon the joint by the body's own immune system." See, the Specification, page 2, lines 22-23.

Although DHEA has some immunologic ability, it is significantly less than that of Δ5-androstene-3β-ol-7,17-dione, as discussed at length above (Section II.). Even if some immune

enhancement is not counter productive to treatment, taken as a whole there is no reason to believe that more is better.

Accordingly, based on Lardy, one of ordinary skill in the art would expect that administration of Δ5-androstene-3β-ol-7,17-dione (an immune enhancer) would exacerbate, rather than treat, arthritis. Such a teaching away from the claimed invention is a significant factor to be considered in determining obviousness and cannot be ignored.

In summary, the requirement for making a prima facie case of obviousness has not been met. In view of the above, Applicant respectfully requests that the obviousness rejection under 35 U.S.C. § 103(a) be withdrawn and that the claims be allowed.

Summary

Applicants assert that the claimed invention is in condition for allowance and respectfully request that the rejection of claims 1-11, 22-29, 31 and 32 be withdrawn. Notification to this effect is respectfully requested.

Any fees due in relation to the timely filing of this Appeal Brief are hereby authorized to be deducted from Deposit Account No. 501536.

Respectfully submitted,

Date: May 16, 2003

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Appendix

1. A method of treating or preventing arthritis in a patient in need of such treatment or prevention, comprising administering to said patient a steroid selected from the group consisting of Δ5-androstene-3β-ol-7,17-dione and 3β esters thereof, wherein said administration results in amelioration or prevention of one or more symptoms of arthritis.

2. The method of claim 1, wherein said steroid is Δ5-androstene-3β-acetoxy-ol-7,17-dione.

3. The method of either one of claims 1 and 2 wherein said patient is human.

4. The method of claim 3, wherein said patient is afflicted with osteoarthritis.

5. The method of claim 3, wherein said patient is afflicted with fibromyalgia.

6. The method of claim 3, wherein said patient is afflicted with rheumatoid arthritis.

7. The method of claim 3, wherein said patient is afflicted with arthritis-related tissue inflammation. collateral to

8. The method of claim 3, wherein said patient is diagnosed with osteoarthritis.

9. The method of claim 3, wherein said patient is diagnosed with fibromyalgia.

10. The method of claim 3, wherein said patient is diagnosed with rheumatoid arthritis.

11. The method of claim 3, wherein said patient is diagnosed with arthritis-related tissue inflammation.

22. The method of either one of claims 1 and 2, wherein said one or more symptoms of arthritis are selected from the group consisting of tissue inflammation, joint pain, joint stiffness, inability to move a joint normally, nodules, and swelling.

23. The method of claim 22, wherein said patient is afflicted with osteoarthritis.

24. The method of claim 22, wherein said patient is afflicted with fibromyalgia.

25. The method of claim 22, wherein said patient is afflicted with rheumatoid arthritis.

26. The method of claim 22, wherein said patient is afflicted with arthritis-related tissue inflammation.

27. The method of claim 22, wherein said patient is diagnosed with osteoarthritis.

28. The method of claim 22, wherein said patient is diagnosed with fibromyalgia.

29. The method of claim 22, wherein said patient is diagnosed with rheumatoid arthritis.

31. The method of claim 3, wherein said steroid is administered by the route selected from the group consisting of intravenous injection, mucosal administration, oral consumption, ocular administration, subcutaneous injection, and transdermal administration.

32. The method of claim 31, wherein said mucosal administration includes routes selected from the group consisting of buccal, endotracheal, inhalation, nasal, pharyngeal, rectal, sublingual and vaginal.

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Real Party in Interest

Humanetics Corporation, a corporation with its principle place of business at Interchange Tower, Suite 1205, 600 South Highway 169, St. Louis Park, MN 55426-1205 is the Real Party in Interest.

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No other appeals or interferences are known to appellant, appellant's legal representative, or assignee that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

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5. Issues

Whether claims 22-29, drawn to methods of treating or preventing arthritis using Δ5-androstene-3β-ol-7,17-dione and 3β esters thereof, in which the one or more symptoms of arthritis are limited to those symptoms selected from the group consisting of tissue inflammation, joint pain, joint stiffness, inability to move a joint normally, nodules, and swelling, are unpatentable under 37 C.F.R. § 1.75(c) for failing to further limit the method recited in claim 1 or 2, in which the one or more symptoms of arthritis are not limited.

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<u>The Claimed Invention is in Proper Dependent Form under 37 C.F.R. § 1.75(c)</u>

Claims 22-29, drawn to methods of treating or preventing arthritis using Δ5-androstene-3β-ol-7,17-dione and 3β esters thereof, in which the one or more symptoms of arthritis are limited to those symptoms selected from the group consisting of tissue inflammation, joint pain, joint stiffness, inability to

move a joint normally, nodules, and swelling, are in proper dependent form under 37 C.F.R. § 1.75(c), because they further limit the method recited in claim 1 or 2, in which the one or more symptoms are not limited.

The Examiner states that "The method of claim 22 is directed to a method of treating arthritis, i.e., the inflammation of the joint. "Tissue inflammation" as recited in claim 22 encompasses inflammatory sites other than joints and thus, fail[s] to further limit the preceding claim." See, Paper 11, page 3, lines 13-15.

This argument fails for at least two reasons: (1) arthritis includes inflammation at sites other than the joint, and (2) "tissue inflammation" is a subset of the many possible "one or more symptoms of arthritis" and so further limits the preceding claim.

A. Arthritis is Not Limited to Joint Inflammation

A "method of treating arthritis" is broader than a "method of treating the inflammation of the joint". The specification states that "Arthritis is a collective term for a number of different conditions that cause pain, swelling and limited movement in joints and connective tissue throughout the body." See, the Specification, page 1, lines 14-15, Emphasis added. Although osteoarthritis is linked to specifically to joint disease and the breakdown of the joint's cartilage, "Fibromyalgia (FM) is manifest as widespread pain affecting muscles and attachments to the bone." See, the Specification, page 1, lines 26-27 and page 2, lines 11-12, Emphasis added. Further, the autoimmune disorder aspect of rheumatoid arthritis "is generally characterized by inflammation of the membrane lining the joint." See, the specification, page 2, lines 20-22, Emphasis added.

Thus, arthritis is not limited to joint inflammation, but encompasses tissue inflammation at sites other than the joints, including connective tissue, muscles, attachments to bone, and membrane linings.

B. Tissue Inflammation Further Limits One or More Symptoms

Independent claim 1 states in part, "wherein said administration results in amelioration or prevention of one or more symptoms of arthritis." Dependent claim 22 states in part, "wherein said one or more symptoms of arthritis are selected from the group consisting of tissue inflammation, join pain, joint stiffness, inability to move a joint normally, nodules, and swelling." Claims 23-29 depend from claim 22. See, Appendix.

The fact that arthritis is not limited to joint inflammation, but also encompasses other forms of tissue inflammation has been discussed above (Section A). In addition, symptoms of arthritis include far more than just tissue inflammation, including, but not limited to, "pain, swelling and limited movement", "fatigue, sleep disturbances, migraine headaches, irritated bowel syndrome, chest pain and nervous system symptoms", and "nodules under the skin." See, the Specification, page 1, lines 14-15 and page 2, lines 13-15 and 31.

Therefore, dependent claims 22-29 further limit claim 1 or 2, and therefore the objection should be withdrawn and the claims allowed.

The Claimed Invention is Not Indefinite under 35 U.S.C. § 112, Second Paragraph

Claims 7, 11 and 26, drawn to methods of treating or preventing arthritis using Δ5-androstene-3β-ol-7,17-dione and 3β esters thereof, in patients that are either afflicted or diagnosed with arthritis-related tissue inflammation, are not indefinite under 35 U.S.C. § 112, second paragraph, because it is clear which patient populations are encompassed by the claims.

The Examiner states that "It is not clear what tissue inflammation conditions are encompassed by the expression herein and therefore, it is not clear what patient populations are encompassed hereby." See, Paper 11, page 4, lines 3-5 and 8-10.

This argument fails, because it is clear from the claim language (arthritis-related tissue inflammation) that the tissue inflammation conditions are those related to arthritis. Thus, the patient populations are those arthritis patients with tissue inflammation related to their arthritis.

Claims 7, 11, and 26 are ultimately dependent on claim 1, which states in part, "A method of treating or preventing arthritis in a patient in need of such treatment or prevention." Claims 7, 11 and 26 all further limit the patients described in claim 1, to a patient either diagnosed or afflicted with "arthritis-related tissue inflammation." See, Appendix.

Thus, all of these patients are defined by their need for arthritis treatment or prevention according to claim 1, and then are further defined in the dependent claims by the fact that they are either afflicted or diagnosed with tissue inflammation related to their arthritic condition. As a result, claims 7, 11 and 26 clearly identify the claimed subject matter, and therefore the rejections under 35 U.S.C. § 112, second paragraph, for indefiniteness should be withdrawn and the claims amended.

The Examiner has Failed to Prove a *Prima Facie* Case of Obviousness under 35 U.S.C. § 103(a) Based on the Disclosure in Lardy in View of Peat

Claims 1-11, 22-29, 31 and 32, drawn to methods of treating or preventing arthritis using Δ5-androstene-3β-ol-7,17-dione and 3β esters thereof, are patentable and are not obvious under 35 U.S.C. § 103(a) based on the disclosure in Lardy (U.S. Patent No. 5,585,371) of a comparison of the immunological activity of Δ5-androstene-3β-ol-7,17-dione and dehydroepiandrosterone (DHEA) and in view of the disclosure in Peat (U.S. Patent No. 4,628,052) of the utility of DHEA for osteoarthritis, rheumatoid arthritis, and non-specific joint pain.

Three criteria must be met to establish a case of *prima facie* obviousness: (1) there must be some suggestion or

motivation to modify or combine references, (2) there must be a reasonable expectation of success, and (3) the references must teach or suggest all the claim limitations. The teaching or suggestion to make the combination and the reasonable expectation of success must both be found in the cited art, not the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

A reasonable reading of the cited references (Lardy and Peat) indicates that taken together they satisfy none of the three criteria stated above.

I. Lardy and Peat do Not Teach or Suggest All the Claim Limitations.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974).

The claimed invention is drawn *inter alia* to methods of treating arthritis by administering Δ5-androstene-3β-ol-7,17-dione and β esters thereof. These compounds are essentially incapable of being metabolized to androgens, estrogens or DHEA See, for example, the Specification, page 4, lines 18-22.

These claim limitations are neither taught nor suggested by the cited art.

A. The Cited Art Does Not Teach All Claim Limitations

The Examiner states that "Lardy does not expressly teach that [Δ5-androstene-3β-ol-7,17-dione] is useful in a method to treat arthritis such as osteoarthritis, fibromyalgia, and rheumatoid arthritis. Peat teaches that DHEA is useful in a method of osteoarthritis, rheumatoid arthritis, and non-specific joint pain." See, Paper 11, page 5, lines 4-7.

Taken together, these statements show that the Examiner acknowledges that the cited art does not teach treating arthritis

by administering Δ5-androstene-3β-ol-7,17-dione and β esters thereof. Thus, the requirement for teaching all claims limitations is not met.

B. The Cited Art Does Not Suggest All Claim Limitations

In addition to not teaching all the claim limitations, the cited art does not suggest all the claim limitations. Moreover, the Examiner does not provide a reasoned explanation for how the cited art taken together allegedly suggests all the claim limitations.

However, taken together, Peat and Lardy, at most, teach treating arthritis using DHEA, a compound DHEA with significant androgenic ability and some immune stimulating ability. DHEA is the major androgen precursor in men and women. See, for example, the Specification, page 3, lines 21-22. DHEA has some ability to improve antibody responsiveness of the immune system. See, for example, Lardy, column 10, lines 31-33. DHEA is taught for osteoarthritis, rheumatoid arthritis, and non-specific joint pain. See, Peat, abstract.

Therefore, taken together, Peat and Lardy do not suggest using Δ5-androstene-3β-ol-7,17-dione for arthritis. Δ5-androstene-3β-ol-7,17-dione, unlike DHEA, does not have significant androgenic ability. See, for example, the Specification, page 4, lines 18-22. Further, Δ5-androstene-3β-ol-7,17-dione, unlike DHEA, has superior immunologic activity. See, for example, Lardy, column 10, lines 31-33.

Thus, Lardy and Peat do not teach or suggest all the claim limitations of a method to treat or prevent arthritis using a compound without androgenic potential and with immuno-stimulatory potential. Therefore, the Examiner has failed to make a prima facie case for obviousness, and this rejection cannot stand.

II. Lardy and Peat Provide No Suggestion or Motivation to Modify or Combine References.

Obviousness can only be established by combining or modifying teachings where there is some teaching, suggestion or motivation to do so found either in the reference or in the general knowledge of one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992).

The Examiner states that, "It is known that both DHEA and [Δ5-androstene-3β-ol-7,17-dione] have similar immunological effect[,] and based on Lardy, DHEA is known to be useful in [a] method of treating [the] painful condition of osteoarthritis and rheumatoid arthritis." *See*, Paper 11, page 5, lines 11-15.

This argument fails because the Examiner has mischaracterized the cited art. In fact, Lardy teaches that Δ5-androstene-3β-ol-7,17-dione has superior immunologic activity compared to DHEA.

A fair reading of Lardy provides objective evidence that DHEA and Δ5-androstene-3β-ol-7,17-dione do not function similarly as immune response affecting agents. In Example VI (Immune System Response of Δ5-androstene-3β-ol-7,17-dione), the data show that treatment with Δ5-androstene-3β-ol-7,17-dione decreased mortality from a herpes infection to 26%, while DHEA treated animals showed little to no difference from untreated control animals (67% compared to 80%). Under "Conclusions," Lardy writes, "Administration of Δ5-androstene-3β-ol-7,17-dione substantially enhances immune response relative to normal response. Δ5-androstene-3β-ol-7,17-dione is also substantially superior to DHEA in enhancement of immune system response." See, Lardy, column 10, lines 1-33.

Clearly, a compound that acts in a superior manner to another compound does not function similarly, and so this motivation to modify or combine references fails. Therefore, the

cited art does not provide a suggestion or motivation to modify or combine references to achieve the claimed method to treat or prevent arthritis using a compound with superior immuno-stimulatory potential. Therefore, the Examiner has failed to make a prima facie case for obviousness, and this rejection cannot stand.

III. Lardy and Peat do Not Indicate that there is a Reasonable Expectation of Success.

The cited art can be modified or combined to reject claims as *prima facie* obvious only if there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 U.S.P.Q. 375 (Fed. Cir. 1986).

The Examiner states that, "Employing [Δ5-androstene-3β-ol-7,17-dione], a structurally similar compound [that] also has similar pharmacological activities as DHEA, in the same method [as] Peat to treat arthritis...would have been reasonably expected to be similarly effective." See, Paper 11, page 5, lines 15-18.

This argument fails for at least two reasons: (1) because steroid hormone activity can be structure specific, and (2) because DHEA and Δ5-androstene-3β-ol-7,17-dione have different pharmacological activities.

A. Steroid Hormone Activity can be Structure Specific

Steroid hormone activity can be structure specific, such that the activity of structurally related species can be difficult to predict. *See, for example, Ortho Pharmaceutical Corp. v. Smith*, 22 U.S.P.Q. 1119, 1125 (1992) and *Brenner v. Manson*, 148 U.S.P.Q. 689, 694 (1966). Here, the difference between DHEA and Δ5-androstene-3β-ol-7,17-dione is the addition of a ketone at the 7 position. This chemical change results in a compound with no significant androgenic or estrogenic activity, and superior immunological activity as compared to DHEA, that

lacks the ketone at the 7 position (see further discussion below, Section B). Thus, the structural similarity, without more, does not make a *prima facie* case of obviousness.

B. The Pharmacological Activity of DHEA is Different from Δ5-androstene-3β-ol-7,17-dione

The pharmacologic activity of DHEA differs from that of Δ5-androstene-3β-ol-7,17-dione in at least two respects: (1) DHEA is far less active immunologically than Δ5-androstene-3β-ol-7,17-dione, and (2) DHEA has significant androgenic and estrogenic activity that is lacking in Δ5-androstene-3β-ol-7,17-dione.

The superiority of Δ5-androstene-3β-ol-7,17-dione over DHEA immunologically (based on Lardy) have been discussed at length above (Section II). Clearly, a compound that is immunologically superior to another compound, will not be expected to have similar pharmacological effects.

A known pharmacological activity of DHEA is as an androgen and estrogen precursor. DHEA is the major androgen precursor in men and women. See, for example, the Specification, page 3, lines 21-22. Unlike DHEA, Δ5-androstene-3β-ol-7,17-dione does not have significant androgenic ability. See, for example, the Specification, page 4, lines 18-22. Clearly, a compound that is not appreciably metabolized to androgens, will not be expected to have similar pharmacological effects as a compound that is the major androgen precursor.

Thus, taken as a whole, the cited art does not indicate a reasonable expectation of success. Thus, the requirement for making a prima facie case of obviousness has not been met.

IV. The Art Teaches Away from the Claimed Invention

A *prima facie* case of obviousness can also be rebutted by showing that the art, in any material respect, teaches away from

the claimed invention. *In re Geisler*, 116 F.3d 1465, 1471, 43 U.S.P.Q.2d 1362, 1366 (Fed. Cir. 1977).

Here, the art teaches away in at least two material respects: (1) DHEA's usefulness for treating arthritis would be predicted to relate to its androgenic or estrogenic activity, which is absent in Δ5-androstene-3β-ol-7,17-dione, and (2) Δ5-androstene-3β-ol-7,17-dione's superior immunological activity, compared to DHEA, would be counter-intuitive for treating arthritis.

A. Lack of Significant Androgenic or Estrogenic Activity Teaches Away

DHEA is the major androgen precursor in humans, and is responsible for pleiotropic effects in humans. Δ5-androstene-3β-ol-7,17-dione is not significantly metabolizable to androgens, including DHEA, and does not have androgenic effects in humans. See, for example, the Specification, page 3, lines 21-22 and page 4, lines 18-22.

Since low androgen levels have been linked to arthritis, a compound that raised androgen levels (like DHEA) would be predicted to be beneficial. In contrast, the lack of androgenic activity resulting from Δ5-androstene-3β-ol-7,17-dione administration would teach away from its use in arthritis.

In rheumatoid arthritis (RA), for example, androgen levels are low in both men and women. In addition, RA is characterized by striking age-sex disparities. The incidence of RA in women increases steadily from the age of menarche to its maximal incidence around menopause. The disease is uncommon in men under 45, but its incidence increases rapidly in older men and eventually approaches the incidence in women. These events correlate with dramatic changes in androgen levels in men and women. These observations strongly suggest that androgens may play some role in RA. See, for example, the Specification, page 3, lines 16-31.

Furthermore, since elevated levels of female sex hormones (estrogens) have been linked to remission of arthritis in pregnancy, a compound that raised estrogenic levels (like DHEA) would be predicted to be beneficial. Moreover, DHEA itself has been found to be present in elevated quantities during pregnancy, providing additional reason to predict benefit. See, Peat, column 1, lines 36-46. In contrast, the lack of estrogenic activity resulting from Δ5-androstene-3β-ol-7,17-dione administration would teach away from its use in arthritis.

Thus, one of ordinary skill in the art would be likely to conclude that DHEA's activity in arthritis may well be the result of its androgenic or estrogenic ability. Since Δ5-androstene-3β-ol-7,17-dione lacks androgenic and estrogenic activity, Peat teaches away from the use of Δ5-androstene-3β-ol-7,17-dione to treat arthritis.

B. Superior Immunological Activity Teaches Away

Enhancing immune function and particularly improving the immune response to an antigen, is counterintuitive as a treatment for arthritis. Arthritis is a disorder with inflammatory components. It is typically treated with anti-inflammatory drugs. See, the Specification, page 2, lines 4-9 describing conventional treatment for osteoarthritis; page 2, lines 17-18 describing conventional treatment for fibromyalgia; and page 3, lines 8-14 describing conventional treatment for rheumatoid arthritis. Further, rheumatoid arthritis has an autoimmune aspect "generally characterized by inflammation of the membrane lining the joint resulting from an attack upon the joint by the body's own immune system." See, the Specification, page 2, lines 22-23.

Although DHEA has some immunologic ability, it is significantly less than that of Δ5-androstene-3β-ol-7,17-dione, as discussed at length above (Section II.). Even if some immune

enhancement is not counter productive to treatment, taken as a whole there is no reason to believe that more is better.

Accordingly, based on Lardy, one of ordinary skill in the art would expect that administration of Δ5-androstene-3β-ol-7,17-dione (an immune enhancer) would exacerbate, rather than treat, arthritis. Such a teaching away from the claimed invention is a significant factor to be considered in determining obviousness and cannot be ignored.

In summary, the requirement for making a prima facie case of obviousness has not been met. In view of the above, Applicant respectfully requests that the obviousness rejection under 35 U.S.C. § 103(a) be withdrawn and that the claims be allowed.

Summary

Applicants assert that the claimed invention is in condition for allowance and respectfully request that the rejection of claims 1-11, 22-29, 31 and 32 be withdrawn. Notification to this effect is respectfully requested.

Any fees due in relation to the timely filing of this Appeal Brief are hereby authorized to be deducted from Deposit Account No. 501536.

Respectfully submitted,

Date: May 16, 2003

By: Heather L. Callahan
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Appendix

1. A method of treating or preventing arthritis in a patient in need of such treatment or prevention, comprising administering to said patient a steroid selected from the group consisting of Δ5-androstene-3β-ol-7,17-dione and 3β esters thereof, wherein said administration results in amelioration or prevention of one or more symptoms of arthritis.

2. The method of claim 1, wherein said steroid is Δ5-androstene-3β-acetoxy-ol-7,17-dione.

3. The method of either one of claims 1 and 2 wherein said patient is human.

4. The method of claim 3, wherein said patient is afflicted with osteoarthritis.

5. The method of claim 3, wherein said patient is afflicted with fibromyalgia.

6. The method of claim 3, wherein said patient is afflicted with rheumatoid arthritis.

7. The method of claim 3, wherein said patient is afflicted with arthritis-related tissue inflammation.

8. The method of claim 3, wherein said patient is diagnosed with osteoarthritis.

9. The method of claim 3, wherein said patient is diagnosed with fibromyalgia.

10. The method of claim 3, wherein said patient is diagnosed with rheumatoid arthritis.

11. The method of claim 3, wherein said patient is diagnosed with arthritis-related tissue inflammation.

22. The method of either one of claims 1 and 2, wherein said one or more symptoms of arthritis are selected from the group consisting of tissue inflammation, joint pain, joint stiffness, inability to move a joint normally, nodules, and swelling.

23. The method of claim 22, wherein said patient is afflicted with osteoarthritis.

24. The method of claim 22, wherein said patient is afflicted with fibromyalgia.

25. The method of claim 22, wherein said patient is afflicted with rheumatoid arthritis.

26. The method of claim 22, wherein said patient is afflicted with arthritis-related tissue inflammation.

27. The method of claim 22, wherein said patient is diagnosed with osteoarthritis.

28. The method of claim 22, wherein said patient is diagnosed with fibromyalgia.

29. The method of claim 22, wherein said patient is diagnosed with rheumatoid arthritis.

31. The method of claim 3, wherein said steroid is administered by the route selected from the group consisting of intravenous injection, mucosal administration, oral consumption, ocular administration, subcutaneous injection, and transdermal administration.

32. The method of claim 31, wherein said mucosal administration includes routes selected from the group consisting of buccal, endotracheal, inhalation, nasal, pharyngeal, rectal, sublingual and vaginal.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:Weeks
Application No.	:09/554,951
Filed	:November 27, 2000
For	: THE USE OF Δ5-ANDROSTENE-3β-OL-7,17-DIONE IN THE TREATMENT OF ARTHRITIS
Examiner	:Hui, San-ming
Group Art Unit	:1617

APPEAL BRIEF IN TRIPLICATE UNDER 37 C.F.R. § 1.192

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to the Final Office Action, dated July 16, 2002, the Advisory Action, dated January 29, 2003, and the Notice of Appeal, dated December 13, 2002, for the above-referenced application, the following timely Appeal Brief in triplicate is respectfully submitted.

Authorities

Patents

Lardy, U.S. Patent No. 5,585,371

Peat, U.S. Patent No. 4,628,052

Cases

Brenner v. Manson, 148 U.S.P.Q. 689 (C.C.P.A. 1966)

In re Fine, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988)

In re Geisler, 116 F.3d 1465, 43 U.S.P.Q.2d 1362 (Fed. Cir. 1977)

In re Jones, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992)

In re Merck & Co., Inc., 800 F.2d 1091, 231 U.S.P.Q. 375 (Fed. Cir. 1986)

Ortho Pharmaceutical Corp. v. Smith, 22 U.S.P.Q.2d 1119 (Fed. Cir. 1992)

In re Royka, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974)

In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991)

Real Party in Interest

Humanetics Corporation, a corporation with its principle place of business at Interchange Tower, Suite 1205, 600 South Highway 169, St. Louis Park, MN 55426-1205 is the Real Party in Interest.

1. Related Appeals and Interferences

No other appeals or interferences are known to appellant, appellant's legal representative, or assignee that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

2. Status of Claims

Claims 1-11 and 22-38 are pending. Claims 1-11 and 22-38 stand rejected.

The rejection of claims 1-11, 22-29, 31 and 32 is hereby appealed.

3. Status of Amendments

The proposed amendments provided in the Response to Final Office Action, dated December 13, 2002, were not entered. The claim objections under 37 C.F.R. § 1.75(c), and the claim rejections under 35 U.S.C. § 112, second paragraph and 35 U.S.C. § 103(a), remain.

4. Summary of Invention

The instant invention is drawn to methods of treating or preventing arthritis using Δ5-androstene-3β-ol-7,17-dione and 3β esters thereof. (See, the "Summary of Invention", page 4, lines 8-12; and the "Detailed Description of the Invention" page 4, lines 18-22 and page 5, lines 4-11).

5. Issues

Whether claims 22-29, drawn to methods of treating or preventing arthritis using Δ5-androstene-3β-ol-7,17-dione and 3β esters thereof, in which the one or more symptoms of arthritis are limited to those symptoms selected from the group consisting of tissue inflammation, joint pain, joint stiffness, inability to move a joint normally, nodules, and swelling, are unpatentable under 37 C.F.R. § 1.75(c) for failing to further limit the method recited in claim 1 or 2, in which the one or more symptoms of arthritis are not limited.

Whether claims 7, 11 and 26, drawn to methods of treating or preventing arthritis using Δ5-androstene-3β-ol-7,17-dione and 3β esters thereof, in patients that are either afflicted or diagnosed with arthritis-related tissue inflammation, are unpatentable under 35 U.S.C. § 112, second paragraph, for indefiniteness as to what patients are encompassed by the claims.

Whether claims 1-11, 22-29, 31 and 32, drawn to methods of treating or preventing arthritis using Δ5-androstene-3β-ol-7,17-dione and 3β esters thereof, are unpatentable under 35 U.S.C. § 103(a) for obviousness based on the disclosure in Lardy (U.S. Patent No. 5,585,371) in view of Peat (U.S. Patent No. 4,628,052).

6. Grouping of Claims

All of the claims stand or fall together.

7. Argument

<u>The Claimed Invention is in Proper Dependent Form under 37 C.F.R. § 1.75(c)</u>

Claims 22-29, drawn to methods of treating or preventing arthritis using Δ5-androstene-3β-ol-7,17-dione and 3β esters thereof, in which the one or more symptoms of arthritis are limited to those symptoms selected from the group consisting of tissue inflammation, joint pain, joint stiffness, inability to

move a joint normally, nodules, and swelling, are in proper dependent form under 37 C.F.R. § 1.75(c), because they further limit the method recited in claim 1 or 2, in which the one or more symptoms are not limited.

The Examiner states that "The method of claim 22 is directed to a method of treating arthritis, i.e., the inflammation of the joint. "Tissue inflammation" as recited in claim 22 encompasses inflammatory sites other than joints and thus, fail[s] to further limit the preceding claim." See, Paper 11, page 3, lines 13-15.

This argument fails for at least two reasons: (1) arthritis includes inflammation at sites other than the joint, and (2) "tissue inflammation" is a subset of the many possible "one or more symptoms of arthritis" and so further limits the preceding claim.

A. Arthritis is Not Limited to Joint Inflammation

A "method of treating arthritis" is broader than a "method of treating the inflammation of the joint". The specification states that "Arthritis is a collective term for a number of different conditions that cause pain, swelling and limited movement in joints and connective tissue throughout the body." See, the Specification, page 1, lines 14-15, Emphasis added. Although osteoarthritis is linked to specifically to joint disease and the breakdown of the joint's cartilage, "Fibromyalgia (FM) is manifest as widespread pain affecting muscles and attachments to the bone." See, the Specification, page 1, lines 26-27 and page 2, lines 11-12, Emphasis added. Further, the autoimmune disorder aspect of rheumatoid arthritis "is generally characterized by inflammation of the membrane lining the joint." See, the specification, page 2, lines 20-22, Emphasis added.

Thus, arthritis is not limited to joint inflammation, but encompasses tissue inflammation at sites other than the joints, including connective tissue, muscles, attachments to bone, and membrane linings.

B. Tissue Inflammation Further Limits One or More Symptoms

Independent claim 1 states in part, "wherein said administration results in amelioration or prevention of one or more symptoms of arthritis." Dependent claim 22 states in part, "wherein said one or more symptoms of arthritis are selected from the group consisting of tissue inflammation, join pain, joint stiffness, inability to move a joint normally, nodules, and swelling." Claims 23-29 depend from claim 22. See, Appendix.

The fact that arthritis is not limited to joint inflammation, but also encompasses other forms of tissue inflammation has been discussed above (Section A). In addition, symptoms of arthritis include far more than just tissue inflammation, including, but not limited to, "pain, swelling and limited movement", "fatigue, sleep disturbances, migraine headaches, irritated bowel syndrome, chest pain and nervous system symptoms", and "nodules under the skin." See, the Specification, page 1, lines 14-15 and page 2, lines 13-15 and 31.

Therefore, dependent claims 22-29 further limit claim 1 or 2, and therefore the objection should be withdrawn and the claims allowed.

The Claimed Invention is Not Indefinite under 35 U.S.C. § 112, Second Paragraph

Claims 7, 11 and 26, drawn to methods of treating or preventing arthritis using Δ5-androstene-3β-ol-7,17-dione and 3β esters thereof, in patients that are either afflicted or diagnosed with arthritis-related tissue inflammation, are not indefinite under 35 U.S.C. § 112, second paragraph, because it is clear which patient populations are encompassed by the claims.

The Examiner states that "It is not clear what tissue inflammation conditions are encompassed by the expression herein and therefore, it is not clear what patient populations are encompassed hereby." See, Paper 11, page 4, lines 3-5 and 8-10.

This argument fails, because it is clear from the claim language (arthritis-related tissue inflammation) that the tissue inflammation conditions are those related to arthritis. Thus, the patient populations are those arthritis patients with tissue inflammation related to their arthritis.

Claims 7, 11, and 26 are ultimately dependent on claim 1, which states in part, "A method of treating or preventing arthritis in a patient in need of such treatment or prevention." Claims 7, 11 and 26 all further limit the patients described in claim 1, to a patient either diagnosed or afflicted with "arthritis-related tissue inflammation." See, Appendix.

Thus, all of these patients are defined by their need for arthritis treatment or prevention according to claim 1, and then are further defined in the dependent claims by the fact that they are either afflicted or diagnosed with tissue inflammation related to their arthritic condition. As a result, claims 7, 11 and 26 clearly identify the claimed subject matter, and therefore the rejections under 35 U.S.C. § 112, second paragraph, for indefiniteness should be withdrawn and the claims amended.

The Examiner has Failed to Prove a *Prima Facie* Case of Obviousness under 35 U.S.C. § 103(a) Based on the Disclosure in Lardy in View of Peat

Claims 1-11, 22-29, 31 and 32, drawn to methods of treating or preventing arthritis using Δ5-androstene-3β-ol-7,17-dione and 3β esters thereof, are patentable and are not obvious under 35 U.S.C. § 103(a) based on the disclosure in Lardy (U.S. Patent No. 5,585,371) of a comparison of the immunological activity of Δ5-androstene-3β-ol-7,17-dione and dehydroepiandrosterone (DHEA) and in view of the disclosure in Peat (U.S. Patent No. 4,628,052) of the utility of DHEA for osteoarthritis, rheumatoid arthritis, and non-specific joint pain.

Three criteria must be met to establish a case of *prima facie* obviousness: (1) there must be some suggestion or

motivation to modify or combine references, (2) there must be a reasonable expectation of success, and (3) the references must teach or suggest all the claim limitations. The teaching or suggestion to make the combination and the reasonable expectation of success must both be found in the cited art, not the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

A reasonable reading of the cited references (Lardy and Peat) indicates that taken together they satisfy none of the three criteria stated above.

I. Lardy and Peat do Not Teach or Suggest All the Claim Limitations.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974).

The claimed invention is drawn *inter alia* to methods of treating arthritis by administering Δ5-androstene-3β-ol-7,17-dione and β esters thereof. These compounds are essentially incapable of being metabolized to androgens, estrogens or DHEA See, for example, the Specification, page 4, lines 18-22.

These claim limitations are neither taught nor suggested by the cited art.

A. The Cited Art Does Not Teach All Claim Limitations

The Examiner states that "Lardy does not expressly teach that [Δ5-androstene-3β-ol-7,17-dione] is useful in a method to treat arthritis such as osteoarthritis, fibromyalgia, and rheumatoid arthritis. Peat teaches that DHEA is useful in a method of osteoarthritis, rheumatoid arthritis, and non-specific joint pain." See, Paper 11, page 5, lines 4-7.

Taken together, these statements show that the Examiner acknowledges that the cited art does not teach treating arthritis

by administering Δ5-androstene-3β-ol-7,17-dione and β esters thereof. Thus, the requirement for teaching all claims limitations is not met.

B. The Cited Art Does Not Suggest All Claim Limitations

In addition to not teaching all the claim limitations, the cited art does not suggest all the claim limitations. Moreover, the Examiner does not provide a reasoned explanation for how the cited art taken together allegedly suggests all the claim limitations.

However, taken together, Peat and Lardy, at most, teach treating arthritis using DHEA, a compound DHEA with significant androgenic ability and some immune stimulating ability. DHEA is the major androgen precursor in men and women. See, for example, the Specification, page 3, lines 21-22. DHEA has some ability to improve antibody responsiveness of the immune system. See, for example, Lardy, column 10, lines 31-33. DHEA is taught for osteoarthritis, rheumatoid arthritis, and non-specific joint pain. See, Peat, abstract.

Therefore, taken together, Peat and Lardy do not suggest using Δ5-androstene-3β-ol-7,17-dione for arthritis. Δ5-androstene-3β-ol-7,17-dione, unlike DHEA, does not have significant androgenic ability. See, for example, the Specification, page 4, lines 18-22. Further, Δ5-androstene-3β-ol-7,17-dione, unlike DHEA, has superior immunologic activity. See, for example, Lardy, column 10, lines 31-33.

Thus, Lardy and Peat do not teach or suggest all the claim limitations of a method to treat or prevent arthritis using a compound without androgenic potential and with immuno-stimulatory potential. Therefore, the Examiner has failed to make a prima facie case for obviousness, and this rejection cannot stand.

II. Lardy and Peat Provide No Suggestion or Motivation to Modify or Combine References.

Obviousness can only be established by combining or modifying teachings where there is some teaching, suggestion or motivation to do so found either in the reference or in the general knowledge of one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992).

The Examiner states that, "It is known that both DHEA and [Δ5-androstene-3β-ol-7,17-dione] have similar immunological effect[,] and based on Lardy, DHEA is known to be useful in [a] method of treating [the] painful condition of osteoarthritis and rheumatoid arthritis." *See*, Paper 11, page 5, lines 11-15.

This argument fails because the Examiner has mischaracterized the cited art. In fact, Lardy teaches that Δ5-androstene-3β-ol-7,17-dione has superior immunologic activity compared to DHEA.

A fair reading of Lardy provides objective evidence that DHEA and Δ5-androstene-3β-ol-7,17-dione do not function similarly as immune response affecting agents. In Example VI (Immune System Response of Δ5-androstene-3β-ol-7,17-dione), the data show that treatment with Δ5-androstene-3β-ol-7,17-dione decreased mortality from a herpes infection to 26%, while DHEA treated animals showed little to no difference from untreated control animals (67% compared to 80%). Under "Conclusions," Lardy writes, "Administration of Δ5-androstene-3β-ol-7,17-dione substantially enhances immune response relative to normal response. Δ5-androstene-3β-ol-7,17-dione is also substantially superior to DHEA in enhancement of immune system response." See, Lardy, column 10, lines 1-33.

Clearly, a compound that acts in a superior manner to another compound does not function similarly, and so this motivation to modify or combine references fails. Therefore, the

cited art does not provide a suggestion or motivation to modify or combine references to achieve the claimed method to treat or prevent arthritis using a compound with superior immuno-stimulatory potential. Therefore, the Examiner has failed to make a prima facie case for obviousness, and this rejection cannot stand.

III. Lardy and Peat do Not Indicate that there is a Reasonable Expectation of Success.

The cited art can be modified or combined to reject claims as *prima facie* obvious only if there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 U.S.P.Q. 375 (Fed. Cir. 1986).

The Examiner states that, "Employing [Δ5-androstene-3β-ol-7,17-dione], a structurally similar compound [that] also has similar pharmacological activities as DHEA, in the same method [as] Peat to treat arthritis...would have been reasonably expected to be similarly effective." See, Paper 11, page 5, lines 15-18.

This argument fails for at least two reasons: (1) because steroid hormone activity can be structure specific, and (2) because DHEA and Δ5-androstene-3β-ol-7,17-dione have different pharmacological activities.

A. Steroid Hormone Activity can be Structure Specific

Steroid hormone activity can be structure specific, such that the activity of structurally related species can be difficult to predict. *See, for example, Ortho Pharmaceutical Corp. v. Smith*, 22 U.S.P.Q. 1119, 1125 (1992) and *Brenner v. Manson*, 148 U.S.P.Q. 689, 694 (1966). Here, the difference between DHEA and Δ5-androstene-3β-ol-7,17-dione is the addition of a ketone at the 7 position. This chemical change results in a compound with no significant androgenic or estrogenic activity, and superior immunological activity as compared to DHEA, that

lacks the ketone at the 7 position (see further discussion below, Section B). Thus, the structural similarity, without more, does not make a *prima facie* case of obviousness.

B. The Pharmacological Activity of DHEA is Different from Δ5-androstene-3β-ol-7,17-dione

The pharmacologic activity of DHEA differs from that of Δ5-androstene-3β-ol-7,17-dione in at least two respects: (1) DHEA is far less active immunologically than Δ5-androstene-3β-ol-7,17-dione, and (2) DHEA has significant androgenic and estrogenic activity that is lacking in Δ5-androstene-3β-ol-7,17-dione.

The superiority of Δ5-androstene-3β-ol-7,17-dione over DHEA immunologically (based on Lardy) have been discussed at length above (Section II). Clearly, a compound that is immunologically superior to another compound, will not be expected to have similar pharmacological effects.

A known pharmacological activity of DHEA is as an androgen and estrogen precursor. DHEA is the major androgen precursor in men and women. See, for example, the Specification, page 3, lines 21-22. Unlike DHEA, Δ5-androstene-3β-ol-7,17-dione does not have significant androgenic ability. See, for example, the Specification, page 4, lines 18-22. Clearly, a compound that is not appreciably metabolized to androgens, will not be expected to have similar pharmacological effects as a compound that is the major androgen precursor.

Thus, taken as a whole, the cited art does not indicate a reasonable expectation of success. Thus, the requirement for making a prima facie case of obviousness has not been met.

IV. The Art Teaches Away from the Claimed Invention

A *prima facie* case of obviousness can also be rebutted by showing that the art, in any material respect, teaches away from

the claimed invention. *In re Geisler*, 116 F.3d 1465, 1471, 43 U.S.P.Q.2d 1362, 1366 (Fed. Cir. 1977).

Here, the art teaches away in at least two material respects: (1) DHEA's usefulness for treating arthritis would be predicted to relate to its androgenic or estrogenic activity, which is absent in Δ5-androstene-3β-ol-7,17-dione, and (2) Δ5-androstene-3β-ol-7,17-dione's superior immunological activity, compared to DHEA, would be counter-intuitive for treating arthritis.

A. Lack of Significant Androgenic or Estrogenic Activity Teaches Away

DHEA is the major androgen precursor in humans, and is responsible for pleiotropic effects in humans. Δ5-androstene-3β-ol-7,17-dione is not significantly metabolizable to androgens, including DHEA, and does not have androgenic effects in humans. See, for example, the Specification, page 3, lines 21-22 and page 4, lines 18-22.

Since low androgen levels have been linked to arthritis, a compound that raised androgen levels (like DHEA) would be predicted to be beneficial. In contrast, the lack of androgenic activity resulting from Δ5-androstene-3β-ol-7,17-dione administration would teach away from its use in arthritis.

In rheumatoid arthritis (RA), for example, androgen levels are low in both men and women. In addition, RA is characterized by striking age-sex disparities. The incidence of RA in women increases steadily from the age of menarche to its maximal incidence around menopause. The disease is uncommon in men under 45, but its incidence increases rapidly in older men and eventually approaches the incidence in women. These events correlate with dramatic changes in androgen levels in men and women. These observations strongly suggest that androgens may play some role in RA. See, for example, the Specification, page 3, lines 16-31.

Furthermore, since elevated levels of female sex hormones (estrogens) have been linked to remission of arthritis in pregnancy, a compound that raised estrogenic levels (like DHEA) would be predicted to be beneficial. Moreover, DHEA itself has been found to be present in elevated quantities during pregnancy, providing additional reason to predict benefit. See, Peat, column 1, lines 36-46. In contrast, the lack of estrogenic activity resulting from Δ5-androstene-3β-ol-7,17-dione administration would teach away from its use in arthritis.

Thus, one of ordinary skill in the art would be likely to conclude that DHEA's activity in arthritis may well be the result of its androgenic or estrogenic ability. Since Δ5-androstene-3β-ol-7,17-dione lacks androgenic and estrogenic activity, Peat teaches away from the use of Δ5-androstene-3β-ol-7,17-dione to treat arthritis.

B. Superior Immunological Activity Teaches Away

Enhancing immune function and particularly improving the immune response to an antigen, is counterintuitive as a treatment for arthritis. Arthritis is a disorder with inflammatory components. It is typically treated with anti-inflammatory drugs. See, the Specification, page 2, lines 4-9 describing conventional treatment for osteoarthritis; page 2, lines 17-18 describing conventional treatment for fibromyalgia; and page 3, lines 8-14 describing conventional treatment for rheumatoid arthritis. Further, rheumatoid arthritis has an autoimmune aspect "generally characterized by inflammation of the membrane lining the joint resulting from an attack upon the joint by the body's own immune system." See, the Specification, page 2, lines 22-23.

Although DHEA has some immunologic ability, it is significantly less than that of Δ5-androstene-3β-ol-7,17-dione, as discussed at length above (Section II.). Even if some immune

enhancement is not counter productive to treatment, taken as a whole there is no reason to believe that more is better.

Accordingly, based on Lardy, one of ordinary skill in the art would expect that administration of Δ5-androstene-3β-ol-7,17-dione (an immune enhancer) would exacerbate, rather than treat, arthritis. Such a teaching away from the claimed invention is a significant factor to be considered in determining obviousness and cannot be ignored.

In summary, the requirement for making a prima facie case of obviousness has not been met. In view of the above, Applicant respectfully requests that the obviousness rejection under 35 U.S.C. § 103(a) be withdrawn and that the claims be allowed.

Summary

Applicants assert that the claimed invention is in condition for allowance and respectfully request that the rejection of claims 1-11, 22-29, 31 and 32 be withdrawn. Notification to this effect is respectfully requested.

Any fees due in relation to the timely filing of this Appeal Brief are hereby authorized to be deducted from Deposit Account No. 501536.

Respectfully submitted,

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Appendix

1. A method of treating or preventing arthritis in a patient in need of such treatment or prevention, comprising administering to said patient a steroid selected from the group consisting of Δ5-androstene-3β-ol-7,17-dione and 3β esters thereof, wherein said administration results in amelioration or prevention of one or more symptoms of arthritis.

2. The method of claim 1, wherein said steroid is Δ5-androstene-3β-acetoxy-ol-7,17-dione.

3. The method of either one of claims 1 and 2 wherein said patient is human.

4. The method of claim 3, wherein said patient is afflicted with osteoarthritis.

5. The method of claim 3, wherein said patient is afflicted with fibromyalgia.

6. The method of claim 3, wherein said patient is afflicted with rheumatoid arthritis.

7. The method of claim 3, wherein said patient is afflicted with arthritis-related tissue inflammation.

8. The method of claim 3, wherein said patient is diagnosed with osteoarthritis.

9. The method of claim 3, wherein said patient is diagnosed with fibromyalgia.

10. The method of claim 3, wherein said patient is diagnosed with rheumatoid arthritis.

11. The method of claim 3, wherein said patient is diagnosed with arthritis-related tissue inflammation.

22. The method of either one of claims 1 and 2, wherein said one or more symptoms of arthritis are selected from the group consisting of tissue inflammation, joint pain, joint stiffness, inability to move a joint normally, nodules, and swelling.

23. The method of claim 22, wherein said patient is afflicted with osteoarthritis.

24. The method of claim 22, wherein said patient is afflicted with fibromyalgia.

25. The method of claim 22, wherein said patient is afflicted with rheumatoid arthritis.

26. The method of claim 22, wherein said patient is afflicted with arthritis-related tissue inflammation.

27. The method of claim 22, wherein said patient is diagnosed with osteoarthritis.

28. The method of claim 22, wherein said patient is diagnosed with fibromyalgia.

29. The method of claim 22, wherein said patient is diagnosed with rheumatoid arthritis.

31. The method of claim 3, wherein said steroid is administered by the route selected from the group consisting of intravenous injection, mucosal administration, oral consumption, ocular administration, subcutaneous injection, and transdermal administration.

32. The method of claim 31, wherein said mucosal administration includes routes selected from the group consisting of buccal, endotracheal, inhalation, nasal, pharyngeal, rectal, sublingual and vaginal.